Heart failure is a common condition, affecting up to 3 per cent of the population aged 45 and older, and is associated with high mortality and poor quality of life. Major diagnostic and therapeutic advances have been made over the past three decades, but international and national audits suggest that many patients are incompletely investigated and treated.

This article will review some key points and recent developments in the diagnosis and treatment of heart failure.

Diagnosis depends on both symptoms and objective evidence of cardiac dysfunction
Clinical features and chest radiography are not sufficient to make a diagnosis of heart failure. Echocardiography is normally the preferred investigation of cardiac function, although other imaging including nuclear medicine gated blood pool studies (multi-gated acquisition scan – MUGA), cardiac magnetic resonance imaging (MRI) and contrast angiography may be useful, especially where echocardiographic image quality is poor.

Low BNP makes heart failure diagnosis unlikely
Heart failure in ambulant patients is an unlikely diagnosis in those with low serum natriuretic peptide levels (B-type natriuretic peptide – BNP <100pg per ml or N-terminal pro-BNP – NTproBNP <400pg per ml), and the recent NICE guideline recommends that one of these peptides be assayed in all patients presenting with suspected heart failure in primary care. Those with low levels will not require further referral for echocardiography. As the natriuretic peptide levels also predict prognosis, those with very high levels need urgent assessment (within two weeks).

Due to costs, despite the NICE guideline, natriuretic peptide testing is not available in all areas at present. It can, however, be very useful in patient care and, with the mandate of NICE guidelines, should be arranged in all areas as a priority.

The diagnosis flowchart from the NICE guideline (see Figure 2) shows the recommended place of natriuretic peptide testing.

Importance of aetiology
Heart failure is a syndrome that can arise as a result of many diverse forms of heart disease, including coronary artery disease, hypertension, valvular disease, congenital disease, viral
heart disease (myocarditis), etc. Therefore, a full diagnosis will require establishment of which disease process led to the heart failure. Routine invasive coronary angiography is not always needed, however, especially where coronary revascularisation is not being considered.

Rather surprisingly, ‘standard’ treatments for ischaemic heart disease (IHD) such as statins (CORONA study) and aspirin are not of proven value in heart failure even when caused by IHD, and the STICH study, likely to be the largest of its kind, of surgical revascularisation of patients with IHD failed to meet its primary end-point of reduction of all-cause mortality, although some secondary end-points were improved.

In light of these findings, noninvasive assessment of aetiology, eg with MRI, CT coronary angiography or nuclear medical techniques, may be preferable in many cases.

Cardiac surgery remains invaluable in heart failure due to valve disease and where there is concomitant angina with symptoms uncontrolled on full medical therapy.

**Ivabradine for use in heart failure**

Based on the results of the SHIFT study (see Figure 3), ivabradine (Procoralan) is approved for use in patients with heart failure NYHA class II–IV and left ventricular systolic dysfunction (ejection fraction <35 per cent) whose resting heart rate was over 75 beats per minute in sinus rhythm, whether treated with a beta-blocker or not. Ninety per cent of patients in the SHIFT study were on beta-blockers, where interestingly the heart rate had to be only >70 to qualify. The greatest benefit was seen in those with higher heart rates.

In clinical practice it may be possible to uptitrate the dose of beta-blocker to get the heart rate <75 in many cases, but there are still many patients where this is not possible due to hypotension and other intolerance, and the use of ivabradine is a significant advance especially for those patients where beta-blockers are genuinely contraindicated.

**Beta-blockers can be used in stable COPD**

Despite popular belief, beta-blockers have been used safely and successfully in heart failure patients with proven COPD with no reversibility of airflow obstruction on spirometry, and the recently updated NICE guideline recommends their use in this situation. A cardioselective agent such as bisoprolol or nebivolol (Nebilet) may be preferable to the less selective carvedilol in this situation.

Lung function laboratories may be more likely to carry out reversibility testing if it is stated on the request that testing is mandated by NICE for this indication!

**Heart failure with preserved ejection fraction**

Patients with heart failure with preserved ejection fraction (HFPEF) can be a heterogeneous group. Despite repeated studies showing that patients admitted with HFPEF have a poor prognosis, often as poor as that for patients with systolic dysfunction, there is still no definite evidence on how to treat HFPEF as yet.

Diuretics should be used for symptomatic benefit and it is sensible to manage any underlying cause if possible, eg hypertension with left ventricular hypertrophy.

The results of the large Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) study of spironolactone have generated much interest since publication in 2014. Disappointingly, the overall trial did not show a reduction of the primary end-point of cardiovascular death, aborted cardiac arrest, or hospitalisation for the management of heart failure. However, post-hoc analysis showed a four-fold difference in event rates between subjects recruited in Eastern Europe and those from the Americas, where spironolactone treatment appeared to cause reduced cardiovascular mortality and hospitalisation. While such post-hoc analysis should be interpreted cautiously, in the absence of other proven treatments the use of spironolactone should be considered, especially for those with recurrent hospital admissions.

**Use of mineralocorticoid receptor antagonists will benefit many patients**

Spironolactone and eplerenone (Inspra) have been established treatments for severe chronic heart failure and for postinfarct heart failure for several years. More recently, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) study has shown great benefit of eplerenone in milder (NYHA Class II) heart failure patients who had left ventricular ejection fraction of <35 per cent, which significantly widens the indication for mineralocorticoid receptor antagonists (MRAs). Overall mortality, as well as hospitalisation for heart failure, was significantly reduced in the eplerenone arm (see Figure 5).

While this will lead to prognostic benefits for many patients, and in the study the incidence of significant adverse events including hyperkalaemia was relatively low, the ‘real-world’ incidence of side-effects from MRAs is considerable and careful monitoring will be needed.

It is important to note that trial participants had to have a serum potassium level of <5.0mmol/L and an estimated glomerular filtration rate (eGFR) of more than 30ml/min/1.73m² body surface area. Specialist nursing and/or pharmacy teams may be ideally placed to carry forward the patient monitoring on treatment.

The expanded indication for MRAs in systolic heart failure has been incorporated into the 2014 NICE acute heart failure guideline, which states that one should be offered to all who are hospitalised. The guideline also emphasises the need for clinical stability for 48 hours prior to hospital discharge and close monitoring of both clinical and biochemical status.

**Deterioration of previously stable patients on treatment should prompt a detailed review**

Patients who are on treatment for heart failure who have been stable on evidence-based treatments can nevertheless deteriorate either acutely or gradually. While this may be due to progression of underlying disease that may not be treatable, there is often a precipitant that may be amenable to medical treatment. A careful and comprehensive review should be carried out.

A full blood count may show anaemia that may be due to gastrointestinal bleeding – particularly common in heart failure...
Figure 2. Heart failure diagnosis flowchart from the NICE guideline 2010

Serum natriuretic peptides
High levels – BNP >400pg/ml (116pmol/L) or NTproBNP >2000pg/ml (236pmol/L)
Raised levels – BNP 100–400pg/ml (29–116pmol/L) or NTproBNP 400–2000pg/ml (47–23pmol/L)
Normal levels – BNP <100pg/ml (29pmol/L) or NTproBNP <400pg/ml (47pmol/L)
patients with poor intestinal perfusion who are taking antithrombotic medication. Urea and electrolytes may show deterioration of renal function. Thyroid function tests may become abnormal, especially in patients taking amiodarone.

An ECG may show new-onset atrial fibrillation that may be amenable to cardioversion and in most heart failure patients is a strong indication for anticoagulation. The ECG may also show evidence of a new ischaemic event or MI, and new conduction abnormalities such as high-degree heart block and new left bundle branch block – now highly treatable with cardiac resynchronisation therapy (CRT – see Figure 6) or biventricular pacing.13

In terms of development of services in the future, rapid availability of such comprehensive reassessment of patients who become unstable should be a priority. Meanwhile, ‘routine’ reviews of patients who have an established diagnosis and who are on evidence-based treatments may be able to be avoided.

Diabetic management may need reviewing
Although less marked than with the now-withdrawn rosiglitazone, pioglitazone14 is also associated with an increased heart failure risk and with fluid retention, and heart failure is now listed as a contraindication to pioglitazone use.

With its lower propensity to cause weight gain than other hypoglycaemic medication, many patients with heart failure are useful treated with metformin. However, particularly vigilant monitoring of renal function is recommended for those on diuretics and other medication for heart failure. NICE recommends that metformin dosage should be reviewed if eGFR falls below 45mL/min/1.73m², and metformin avoided if eGFR falls below 30 due to the risk of lactic acidosis.15

Exercise and rehabilitation
Although the largest study (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training – HF-ACTION)16 showed only small reductions in the primary end-points of mortality and hospitalisation, this and other studies have shown benefits in quality of life and rehabilitation is a key recommendation in the NICE heart failure guideline.

Selected patients may be able to receive intravenous diuretics without hospital admission
With increasing pressure on hospital beds and patients preferring to be treated out of hospital, there is recent evidence that intravenous furosemide can be safely given to ambulatory heart failure patients at a day unit,11 with considerable potential cost savings. This is obviously more applicable to those with worsening chronic fluid overload than those with acute pulmonary oedema. Work is also ongoing to study the use of intravenous diuretics by specialist nurses in patients’ homes.

Priorities change as end of life approaches
Symptom control and avoidance of hospital admissions, which many patients find distressing, take precedence over prognostic issues in patients who are irrevocably approaching the end of life. Many patients may be able to stop ‘prognostic’ medications such as statins and multiple antiplatelet and antithrombotic agents. Subcutaneous furosemide can have a role in selected patients.18

Implantable cardioverter-defibrillators (ICDs) should be deactivated in those who are in the late stages of terminal decline due to heart failure, as attempted defibrillations will be likely to be futile and distressing to both patients and their relatives. However, bradycardia pacing and CRT functions would normally be left activated on a device.

Many of the principles of end of life care in heart failure are common to those in other terminal illnesses, and fortunately access to specialist palliative care is improving in many areas for heart failure patients.

First-line treatment for heart failure may change
New evidence was first presented at the European Society of Cardiology meeting in 2014 which took many (including myself) by surprise. The PARADIGM-HF19 trial of LCZ696, a combination of the angiotensin-II receptor blocker valsartan and the neprilysin inhibitor sacubitril, showed significant superiority for the new product over the ACE inhibitor enalapril. The primary end-point of cardiovascular deaths and heart failure hospitalisation was reduced by 20 per cent; all cause mortality was significantly reduced by 16 per cent. There was also a significant improvement in quality-of-life measures. Given the previous withdrawal from the market of omapatrilat, a drug with some similarities, due to excesses of angioedema, it was reassuring that no excess of serious angioedema was seen.

These unexpectedly good results have led to the Committee for Medicinal Products for Human Use (CHMP) ‘fast tracking’ the approval process, so LCZ696 is anticipated to be marketed in 2015. It is likely to lead to much debate on guideline committees as to whether stable patients taking ACE inhibitors should be changed over, or whether initially it should be used for patients not yet on an ACE inhibitor, and of course we do not yet know

![Figure 3. Incidence of primary end-point (composite of cardiovascular death or hospital admission for worsening heart failure), ivabradine vs placebo](image)
how much it will cost. Nevertheless, it is anticipated that it will have a major influence on the treatment of heart failure going forward.

**Beta-blockers less effective in atrial fibrillation than in sinus rhythm**

Beta-blockers have been a key part of the management of heart failure due to left ventricular systolic dysfunction since trials showing huge benefits emerged in the late 1990s. Although the individual trials included patients with atrial fibrillation (AF) with trends towards less benefit than those in sinus rhythm noted, given that the trials overall showed major benefit for beta-blocker therapy, this was incorporated into guidelines as mandated treatment for patients both in sinus rhythm and AF. However, a recent meta-analysis of individual patient data from 10 randomised trials of beta-blockers versus placebo in heart failure showed the expected benefits in sinus rhythm patients (hazard ratio, HR for mortality 0.73) but not in patients in AF (HR 0.97, \( p=0.73 \)).

**Figure 4.** Recommended management of heart failure from the NICE guideline 2010\(^1\)
On this basis, beta-blockers should no longer be considered obligatory for patients in AF with systolic dysfunction and heart failure; though, they are still useful in those with high ventricular rates and suspected ‘tachycardiomyopathy’ (ie poor left ventricular function due to persistently high heart rates). However, over-vigorous treatment of resting heart rates in AF are best avoided, both in this scenario and indeed in other AF patients, as too low heart rates may be harmful.21

Promising results also for Coenzyme Q10
On a smaller scale, coenzyme Q10 has shown promising results as an adjunctive treatment for heart failure.22 Coenzyme Q10 is an essential cofactor for mitochondrial function and is also a powerful naturally-occurring antioxidant. A low level of myocardial coenzyme Q10 is related to the severity of heart failure. The Q-SYMBOI trial of coenzyme Q10 versus placebo in a well-treated group of 420 patients with heart failure showed a significant reduction in the primary end-point of composite major adverse cardiac events (15 vs 26 per cent) at two years. Overall mortality was also significantly lower, although this was not a pre-specified primary end-point. Larger studies will be needed before practice changes, but these results look promising if they can be replicated for this relatively inexpensive and naturally-occurring product.

Conclusion
The treatment of heart failure has evolved rapidly over the past few years and many aspects of this are considered in this article. Patients are often complex, with multiple co-morbidities, and being under specialist care has been shown to be associated with greater use of evidence-based therapies and improved survival. The evidence base has continued to expand and what is considered standard treatment is likely to continue to change over the coming years.

References

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